--60.(new) The method of claim 46, wherein the antagonist is a ribozyme.--

--61.(new) The method of claim 46, wherein the antagonist is a a small molecule.--

--62.(new) The method of claim 46, wherein the antagonist is a carbohydrate molecule.--

--63.(new) The method of claim 46, wherein the antagonist is a monosaccharide.--

--64.(new) The method of claim 46, wherein the antagonist is a an oligosaccharide.--

--65.(new) The method of claim 46, wherein the antagonist is an antibody.--

--66.(new) The method of claim 46, wherein the antagonist does not affect hemostasis in response to tissue injury in the subject.--

REMARKS

Claims 46-55 are pending. Applicants have amended the specification to include indications of registered trademarks and to correct obvious typographical and clerical errors. Applicants have amended the title to indicate the subject matter claimed.

Claims 47-48 were canceled without prejudice. Claims 46, 49 and 50 were amended and new claims 56-66 were introduced hereinabove.

These amendments raise no issue of new matter. Support for these amendments may be found *inter alia* in the specification. Support for the amendments to claim 46 may be found on page 17, lines 8-19 and on pages 110-112. Support for new claims 58-65 may be found on page 17, lines 15-18. Support for new claims 56-57 may be found on page 111, lines 1-5. Support for new claim 66 may be found on page 110, lines 29-30.

Applicants maintain that these amendments raise no issue of new matter. Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this amendment, claims 46 and 49-66 will be pending and under examination.

Objection to the Title

The Examiner stated that the title of the invention is not descriptive. The Examiner stated that a new title is required that is clearly indicative of the invention to which the claims are now currently directed and make some reference to Factor IXa.

In reply, applicants have amended the title to make reference to the claimed invention and request that the Examiner reconsider and withdraw this ground of objection.

Formal Drawings

The Examiner stated that formal drawings and photographs have been submitted which fail to comply with 37 C.F.R. §1.84.

In reply, applicants request that the Examiner hold this objection in abayence until the indication of allowable subject matter. At

that time, applicants will submit formal drawings which comply with 37 C.F.R. §1.84.

Objection to the specification

The Examiner stated that the application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. The Examiner stated that "BALB/c" is the proper designation of this mouse strain, see page 77 of the specification, for example.

In reply, applicants have reviewed the specification and have amended the specification accordingly hereinabove. Applicants request the Examiner to reconsider and withdraw this ground of objection.

Rejection Under 35 U.S.C. §112, first paragraph - Written description

The Examiner rejected claims 44-56 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner stated that the specification as originally filed does not allegedly provide support for the invention as now claimed: "chemically inactivated Factor IXa". The Examiner stated that neither the specification nor the claims as originally filed set forth the metes and bounds of the above-mentioned chemically inactivated Factor IXa. The Examiner states that the instant claims now recite limitations which were not clearly disclosed in

the specification as-filed, and now change the scope of the instant disclosure as-filed. The Examiner states that such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

The Examiner states that the applicant is required to cancel the new matter in the response to this Office Action. Alternatively, the Examiner states that the applicant is invited to provide sufficient written support for the chemically inactivated Factor IXa indicated above or rely upon the limitations set forth in the specification as filed.

In reply, applicants respectfully traverse the rejection and maintain that the presently claimed invention is fully support and described in the subject specification. Applicants have amended claim 46 which is now directed to a method for treating an ischemic disorder in a subject which comprises administering to the subject an antagonist of Factor IX activity in a pharmaceutically acceptable form in a sufficient amount over a sufficient time period to inhibit coagulation so as to thereby treat the ischemic disorder in the subject, wherein the antagonist is selected from the group consisting of a peptide mimetic, a nucleic acid, a small molecule, a carbohydrate molecule, and an antibody.

For example, applicants direct the Examiner's attention to page 17, lines 8-19 and page 110, line 17 to page 112, wherein antagonists of Factor IX are fully described. Factor IXai (the specification defines this term as: "chemically modified so as to resemble Factor IXa, but which lacks its activity") is utilized in Example 9 on page 110. This form of Factor IXai was administered to subjects (a

mouse model of cerebral ischemia and reperfusion stroke) in Example 9 and shown to result in the animals being "free of intracerebral hemorrhage" in comparison to controls.

Applicants have introduced new claims 56-66 to more particularly point out the presently claimed invention. Antagonists of Factor IX are described in the Detailed Description of the specification on page 17 as set forth hereinabove.

Thus, the claimed invention is fully described in the specification and applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection in view of the discussion and amendments set forth above.

Rejection Under 35 U.S.C. §112, first paragraph - Enablement

The Examiner rejected claims 46-55 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"Chemically" inactivated Factor IXa"

The Examiner stated that the specification does not reasonably provide enablement for a method which comprises administering any chemically inactivated Factor IXa to inhibit coagulation, as encompassed by claims 46-55. The Examiner states that the applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any chemically inactivated Factor

IXa, other than the heat inactivated Factor IX, as disclosed on page 17 of the specification. The Examiner stated that it is not clear that heat inactivation even encompasses chemical inactivation.

The Examiner stated that, furthermore, there is insufficient direction or guidance provided to assist one skilled in the art in the selection of any chemically inactivated Factor IXa, nor is there sufficient evidence provided that all such chemically inactivated Factor IXas could be used in a practical manner in a method to inhibit coagulation so as to thereby treat the ischemic disorder in the subject. The Examiner states that it would require undue experimentation to produce all such possible chemically inactivated Factor IXas without more explicit guidance from the disclosure. The Examiner stated that it would require undue experimentation to investigate all such chemically inactivated Factor IXas with respect to their ability to inhibit coagulation.

Modes of Administration

The Examiner stated that there does not appear to be sufficient evidence that applicants' reliance on a method of intravenous administration of any inactivated Factor IXa to mice in a mouse model of cerebral ischemia disclosed in Example 9, would indicated that the claimed therapeutic modalities based upon the method which comprises administration of a pharmaceutically acceptable form of any inactivated Factor IXa wherein the carrier comprises an aerosol, oral or topical carrier, as encompassed by claim 50, would be effective to inhibit coagulation, commensurate in scope with the claimed invention. Additionally, the Examiner stated that the applicant has not provided sufficient guidance and direction nor

objective evidence that the skilled artisan can deliver a sufficient amount of chemically inactivated Factor IXa in an aerosol, oral or topical carrier as encompassed by claim 50, in treating an ischemic disorder. It was the Examiner's position that ischemia comprises treatintg vascular disorders and the Examiner stated that it would not be predictable that one could deliver a therapeutic effect amount in such disorders other than intravascular routes of administration. The Examiner stated that in the absence of objective evidence to the contrary; aerosol, oral and topical carriers and means of delivery are not enabled for treating ischemia.

The Examiner stated that in view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicants' specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for methods which comprise administering inactivated Factor Ixa to inhibit coagulation so as to thereby treat the ischemic disorder in the subject.

In reply, applicants respectfully traverse the rejection and maintain that the presently claimed invention is fully enabled by the subject specification. Claim 46 has been amended hereinabove and applicants have introduced new claims 56-66 to more particularly point out the claimed invention. Claims 46 and 49-66 are fully enabled by the subject specification.

As to the Examiner's first point regarding "chemically inactivated

Factor IXa, applicants respectfully point out that this subject matter has been canceled from the claims without prejudice. Thus, applicants believe this point has been rendered moot.

Applicants do not concede the correctness of the Examiner's statements, but have amended the claims to more particularly point out the claimed invention. The pending claims are fully enabled by the specification and one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. Antagonists of Factor IX activity are enabled by the subject specification (see sections of the specification as set forth hereinabove). Applicants utilize an antagonist of Factor IX activity in Example 9 of the subject application. Activity of Factor IX is manifested by the active form of Factor IX, Factor IXa. Antagonists, such as a small molecule or a competitive inhibitor, are shown to interfere with the activity of Factor IX and cause a competitive inhibition of the Factor IXa-dependent pathway of coagulation. (See pages 110-112 of the specification.)

As to the Examiner's second point regarding modes of administration, applicants respectfully traverse. Applicants have amended claim 50 without conceding the correctness of the Examiner's position. Thus, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In addition, applicants point out that not "all" embodiments of a claimed invention are required to be enabled as the Examiner requires. (See page 3, second line and fourth line from bottom of page of October 21, 1999 Office Action.) In addition, applicants point out that "working examples" of the claimed invention are not required for patentability. Nevertheless, applicants believe that

the amendments presented hereinabove fully address the Examiner's rejections. Reconsideration and favorable action is respectfully requested.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 46-55 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claims 46-55 are indefinite in the recitation of "chemically inactivated Factor IXa" because its characteristics are not known. The Examiner took the position that it is not clear what type of chemical modifications are indicated and whether such chemical modifications include and/or are limited to those that are a result of heat as indicated on page 17 of the instant specification. The Examiner requested clarification.

In reply, applicants respectfully traverse the rejection. Without conceding the correctness of the Examiner's position, applicants have deleted the phrase "chemically inactiviated" from claim 46. Thus, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 46 and 47, 49-51 and 53-55 under 35 U.S.C. §102(b) as being anticipated by Tijburg et al., (J. Biol. Chem. 266:12067-12074, 1991).

The Examiner stated that Tijburg et al. teache that infusion of

chemically inactivated factor IXa prevented thrombus formation in the tumor vasculature of mice (see entire article especially 12072, column 1, lines 1-10, and page 12068, column, 1, lines 6-21 of Section entitled "Preparation of Coagulation Proteins"). The Examiner stated that the definition of "ischemic disorders" disclosed on page 16 of the instant specification "encompasses and is not limited to a peripheral vascular disorder...or a stroke disorder". Therefore, the Examiner stated that the instant claims read on the method used in the tumor vasculature of mice, as taught by Tijburg. The Examiner stated that Tijburg also teaches an intravenous dosage of a total of 10 ug of chemically inactivated Factor IXa (see entire article, in particular page 12068, last paragraph of column 1, lines 9-12); assuming a mouse weighs 25 grams, then the dosage of chemically inactivated factor IXa taught is 400 ug/kg. The Examiner took the position that the claimed functional limitations would be inherent properties of the referenced methods.

In reply, applicants respectfully traverse the rejection and maintain that Tijburg et al. do not anticipate the claimed invention. Applicants maintain that Tijburg et al. do not anticipate treating an ischemic disorder in a subject as presently claimed. The "formation of intravascular thrombi in tumor bearing animals after administration of TNF" (see page 12067, last sentence of Tijburg et al.) pointed to by the Examiner is merely a by-product of the administration of TNF into the vicinity of a tumor in the mouse. This TNF administration occurs coincident with the administration of Factor IXai and therefore, the mice are not suffering from an ischemic disorder. The mice used are only tumor bearing mice (see 12068, first column, last paragraph of Tijburg et al.) and are not suffering from an ischemic disorder.

Furthermore, Tijburg et al. do not anticipate the administration of an antagonist as presently claimed (e.g., "wherein the antagonist is selected from the group consisting of a peptide mimetic, a nucleic acid, a small molecule, a carbohydrate molecule, and an antibody" as recited in claim 46). Factor IXai is not a peptide mimetic, a nucleic acid, a small molecule, a carbohydrate molecule, or an antibody. Therefore, Tijburg et al. do not anticipate the claimed invention.

Applicants maintain that Tijburg et al. do not anticipate the claimed invention since they do not set forth all elements of the presently claimed invention. Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 46-55 under 35 U.S.C. §103(a) as being unpatentable over Tijburg et al., (J. Biol. Chem. 266:12067-12074, 1991) in view of Moller et al. (CA 2,141,642)see 1449.

The Examiner stated that Tijburg et al. teach as described above. However, the Examiner states that Tijburg et al do not apply their teachings to the breadth of ischemic events encompassed by the instant claims.

The Examiner stated that Moller et al. teach that proteolytic fragments of Factor IXa are able to inhibit the Factor IXa induced decrease of the thrombocyte count in vivo and teach their use in prophylaxis and therapy of thrombotic diseaess (see entire article, in particular pages 1 lines 1-2; page 3 line 25; page 4 lines 1-2

and page 5 lines 10-17).

The Examiner stated that one of ordinary skill in the art at the time the invention was made would have been motivated to administer a chemically inactivated factor IXa as taught by Tijburg for use in tumors, in place of the proteolytic fragments of Factor IXa, as taught by Moller et al., in a method to treat thrombosis as taught by Moller et al., since both the chemically inactivated Factor IXa and the proteolytic fragments of Factor IXa appear to exhibit the same or nearly the same structural and functional properties of inhibiting the activity of endogenous Factor IXa. The Examiner states that the dosages and routes of administration (intravascular) were all known at the time the invention was made and would have depended upon the needs of the subject for a particular ischemia disorder.

The Examiner stated that from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the Examiner stated that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In reply, applicants respectfully traverse the rejection. Tijburg et al. in combination with Moller et al. do not render the claimed invention obvious. Applicants refer the Examiner to the comments regarding Tijburg et al. hereinabove and reiterate that Tijburg et al. administer Factor IXai to mice which are bearing tumors, but which are not suffering from an ischemic disorder. Furthermore, Tijburg et al. do not teach or suggest use of antagonists of Factor

IX as presently claimed. There is only the disclosure of administration of Factor IXai. Antagonists as taught by the subject specification are not disclosed or suggested for treatment of ischemic disorders in subjects.

Moller et al. do not remedy the shortcomings of Tijburg et al. Moller et al. merely discloses proteolytic fragments of Factor IX which are not small molecules, since they are of the molecular weight of 12,000 daltons to 50,000 daltons (see page 5, lines 1-10 of Moller et al.). There is no teaching or suggestion of administering an antagonist as presently claimed.

Applicants further maintain that there is no motivation for one of ordinary skill in the art to combine the references of Tijburg et al. and Moller et al. Tijburg et al. (a paper published in the Journal of Biochemistry) describe a specific phenomena resulting from the infusion of TNF into tumor bearing mice and present observations regarding blood flow and shear as it relates to coagulation following TNF administration. Moller et al. (a Canadian patent application which was published) disclose thrombocyte-stabilizing Factor IX fragments. One of ordinary skill in the art which would have been working in the tumor and TNF area of biochemistry and medicine would not have been motivated to read Moller et al. which relates to "fragments of the coagulation Factor IX...as a substance for stabilizing platelets in vivo." See Moller et al. page 1, lines 3-5. Moller et al. do not hint at treating tumors in subjects.

Applicants maintain that one of ordinary skill in the art would not have been motivated to combine Moller et al. with Tijburg et al. Nevertheless, applicants maintain that such a combination does not

render the claimed invention obvious. Applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

Provisional Obviousness-type Double Patenting Rejection

The Examiner provisionally rejected claims 46-55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09/053,871. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because they both encompass methods of inhibiting coagulation with an inactivated Factor IXa which appear to overlap one another. The Examiner stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner stated that claims 46-55 are directed to an invention not patentably distinct from claims 29-30 of commonly assigned co-pending application 09/053,871. The Examiner stated that specifically, the conflicting claims are patentably distinct from each other because both applications are drawn to the same or nearly the same methods of inhibiting coagulation with inactivated Factor IXa; the former application using chemically inactivated Factor IXa, the latter using inactive recombinant muteins of Factor Ixa.

In reply, applicants respectfully request that the Examiner hold this rejection in abeyance until the indication of allowable subject matter in the subject application. At that time, applicants will either submit a terminal disclaimer or reply with

a sufficient argument in support of non-obviousness.

If a telephone interview would be of assistance in advancing the prosectution of the subject application, appicants' undersigned attorney hereby invites the Examiner to whom the subject application is assigned to telephone at the number provided.

No fee, other than the $435.00 extension of time fee, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Jane M Love 4/21/00

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